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CANCER'S PLACE IN GENERAL BIOLOGY

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The condition which has been called cancer by the laity and the medical profession has been studied by the latter largely from the standpoint of disease. Investigators have considered its great destructive action, cause, prevention and treatment, all of which study has been stimulated by the urgent necessity of its eradication from the ills of man, and not in its relation to the known biologic facts concerning the universal conflict between living normal cells and their natural enemies. In order to approach correctly this biologic phase of the condition it will be necessary to answer the question: What is cancer?

To the pathologist, cancer is a cellular overgrowth which occurs in some multicellular organism, especially in man, and which is characterized by its apparently unlimited proliferation, during which it destroys tissues, and is fatal eventually to the whole organism. This, in general, is the conception held by the members of the medical profession, but to the scientific mind which is interested in and trained in the fundamental or more specific factors operating in living nature, it is neither satisfactory nor sufficient.

An analysis of the condition from such a biologic point of view necessitates also for its elucidation a study of the facts relative to the evolution of multicellular organisms from single cells as units of life. Biologists agree that the cell is the visible unit of life, and that all cells have certain fundamental structural and functional characteristics which are common to all. They further agree that all multicellular beings evolve by a process of division or segmentation of a single cell which has been stimulated automatically, or by the process of extrinsic fertilization to such activity.

During the process of segmentation certain dominant facts present themselves. A fertilized ovum, for exam-

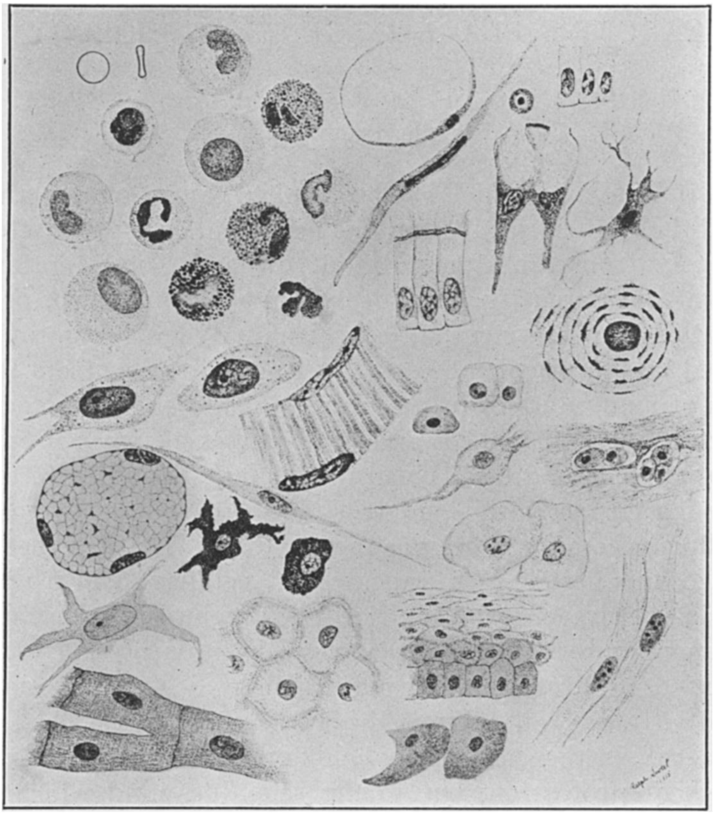

FIG. 1. Some of the differentiated cells (textocytes) of the human body:

Biologic Terminology	*Medical Terminology*
1. Erythrocytes,	Red blood corpuscles.
2. Lymphocytes (small),	Lymphocytes (small).
3. Lymphocytes (large),	Lymphocytes (large).
4. Transitional forms,	Transitional forms.
5. Leukocytes,	Polymorphonuclear leukocytes.
6. Eosinocytes,	Eosinophiles.
7. Mastocytes,	Mast cells.
8. Fibrocytes,	Fibrous connective tissue cells.
9. Rhabdomyocytes,	Striated muscle cells.
10. Melanocytes,	Pigmented cells.
11. Myxocytes,	Muscle cells.
12. Cardiomyocytes,	Heart muscle cells.
13. Lipocytes,	Fat cells.
14. Leiomyocytes,	Smooth muscle cells.
15, 18, 19. Adenocytes,	Glandular epithelium.
16, 24. Neurocytes,	Nerve cells (neurones).
17. Osteocytes,	Bone cells.
20. Endotheliocytes,	Endothelial cells.
21. Chondrocytes,	Cartilage cells.
22. Epitheliocytes,	Epithelial cells.
23. Tendocytes,	Tendon cells.
25. Sudorocytes,	Sweat cells.
26. Sebocytes,	Sebaceous cells.
27. Gustocytes,	Taste cells (of a taste bud).

ple, divides; the cellular divisions divide; these continue to divide and form eventually, in a definite period, the millions of cells which constitute the organism. This is a simple statement of general facts, but coincidentally with these facts there is an orderly sequence of cellular changes which seems to be foreordained in the original fertilized ovum; the cellular progeny does not retain, to the same degree, all of the structural and functional characteristics of the original cell (ovocyte). There is a grouping of cells which is coincident with morphological and functional differences. Out of such differentiation and specialization of cells, types of cells arise, groups of which constitute what are called tissues (adenotex, chondrotex, endotheliotex, epitheliotex, erythrotex, fibrotex, etc.) (Fig. 1). Two or more of the different tissues become grouped to form organs (tongue, esophagus, stomach, liver, kidneys, skin, etc.) which likewise are grouped to build up structural and functional systems (respiratory, alimentary, nervous, osseous, etc.), the combined qualities of which form the complete multicellular organ-

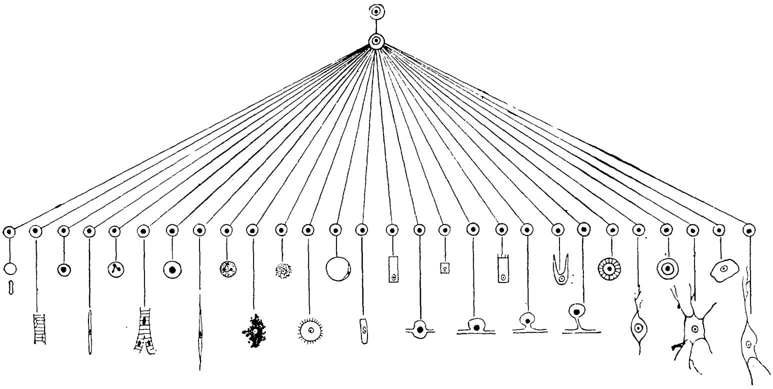

FIG. 2. In the embryonic evolution of adult tissues there are certain arbitrary stages of differentiation in which the cells may be given certain names.

During segmentation of the fertilized ovum (ovocyte) the daughter cells do not show any special morphologic characteristics of adult tissues, but are nevertheless forebearers of such tissues and may be called *protextoblasts*.

The textocytes, or tissue cells, are represented in this diagram by symbols derived from the characteristic outlines of the cells of specific tissues (Fig. 1).

After the protextoblasts align themselves into the positions of subsequent tissues they become the immediate forebearers of the tissues and may be called textoblasts. These cells develop by differentiation and specialization into the tissues (textocytes) of embryonic and adult life. Some of the cells remain undifferentiated (textoblasts) in adult life to form the reserve or regenerative cells for specific tissues when the latter are destroyed.

ism or being. Such orderly evolutional facts apply to the development of all animal and vegetable multicellular beings (Fig. 2).

Out of the essential living properties of a single cell other cells develop which have in them an exaggeration of some essential initial quality, each tissue representing an exaggeration of some one quality. Such evolutionary cytologic organization produces a communism of living units, the combined apparent and dominant purpose of which is to live and reproduce its kind.

A biologist, if asked the ultimate purpose of life, would shake his head and say he did not know, but asked the immediate and dominant purpose, would say the protection of life and this protection even at the expense of life, an apparent contradiction which has been recognized but not comprehended even by scientists. The evidence of this great protective purpose of living matter is too universal to be called to the attention of the least observing; it works automatically and in a large degree independently of the will of living beings.

This fundamental vital protective purpose forms the basis of the following consideration of cancer's place in general biology: It presupposes, and observation substantiates it, that all living cells have natural antagonists against which protection is necessary; and that there is a conflict in nature during which there is constant building up and tearing down of things living. The human body is no exception to this rule, as every physician and layman knows. The tearing down is called disease, and the rebuilding is called regeneration, repair and healing.

The partial destruction of a human tissue by animate or inanimate antagonists may be followed by its regeneration; the complete destruction may be followed by repair or replacement, but not by its regeneration.[1] The degree of regeneration of tissues, according to the observations of biologists, is in an inverse ratio to the degree of their specialization and differentiation. One finds, therefore, this regenerative factor a variable and unequal quantity among tissues of the human body. The protective tissue cells (epitheliocytes) of the skin, for example, are readily regenerated if not completely destroyed over a large area; the cells of the retina, in all probability, are never regenerated even after partial destruction. Fibrocytic, erythrocytic, epitheliocytic and leucocytic tissues, in all probability, represent types, the special functions of which show the highest degrees of regeneration.

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[1] This statement may not seem to be true when applied to some of the lower forms of life such as the earthworm (*Allolobophora fœtida*) and the planaria, in which organizations certain tissues are regenerated after apparent complete destruction. The destruction is, however, not complete in such cases, because the normal regenerative power resides in other cells, which by the process of metaplasia build up tissues they do not form in the normal sequence of evolution.

In many tissues of the body, coincidentally to normal communistic activity, there is constant or periodic normal destruction with constant or periodic regeneration, both of which depend on communistic functional activity and a constant or periodic destructive action of antagonistic agents. The amount of regeneration depends on the amount of destruction, which depends on the quality, quantity and duration of action of the destructive agent or agents.

Tissue destruction and regeneration were made the subject of investigation by the writer, in the protective cells of the human skin (Fig. 3) and in the secretory epithelium of the human mammary gland (Fig. 4). One finds in these organs that some unknown irritant or irritants of an apparent low degree of virulence, acting over a prolonged period of time, produce certain reactive cellular phenomena; there is first a destruction of the specialized and differentiated cells (textocytes). This destruction is associated with an hypertrophy of the so-called basal cells (cells of the stratum germinativum, or textoblasts) and a lymphocytic infiltration in the supporting stroma.

Space does not permit a consideration of the factor of lymphocytic infiltration. The hypertrophy of the so-called basal cells, however, is of great importance from the standpoint of the subject under consideration.

One sees clearly that nature, in building up the special-

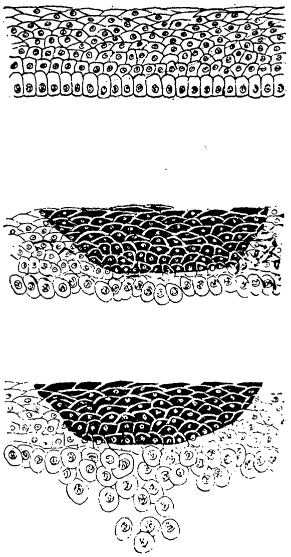


FIG. 3. Three diagrammatic histologic stages of reaction of textoblasts of the epithelium of the skin under normal and certain destructive conditions. (*a*) Normal epithelium showing the relative position of textocytes and textoblasts. (*b*) Destruction of the textocytes is indicated by the shaded portion. The response to chronic destruction is an hypertrophy or an hyperplasia of the textoblasts. This hyperplasia takes place with and without differentiation into textocytes, depending on the degree and chronicity of the destruction. In this condition it is impossible to state from the morphologic appearance whether the cells will become differentiated or remain undifferentiated. (*c*) Represents the stage of migration of the hyperplastic undifferentiated textoblasts.

ized and differentiated protective cells of the skin and the secretory cells of the mammary gland, has also made provision for an anticipated destruction, an anticipation which is no more remarkable in nature than that of the butterfly which deposits its eggs in a safe place and dies with the inherent assuredness that the eggs will some day develop into caterpillars and eventually into butterflies to continue the existence of the kind. In the case of the cells of the skin and the mammary gland, if the irritant is removed, complete regeneration of differentiated or specialized cells takes place, provided the basal cells themselves have not been completely destroyed.

Continuance of the action of the destructive agent or agents produces hypertrophy, hyperplasia and migration of the basal or regenerative cells (Figs 3 and 4). Coincidentally with such a hyperplasia the basal cells (textoblasts) do not always become differentiated to the form of the specialized squamous or secretory cells according to their communistic normal foreordination; they retain their oval or spheroidal form, become larger and produce a massed overgrowth of undifferentiated cells (Figs. 3 and 4). The degree of hyperplasia and migration varies under different and perhaps the same irritative circumstances, depending on inherited variable factors in the basal cells the neighboring tissue cells, their food supply, natural drainage, and perhaps some unknown factors. The significant biologic facts rest in the attempted cellular regeneration by hypertrophy and hyperplasia and the effort to change environment by migration, all of which may be seen not only in the breast and skin, but also in the specific cells of the hair follicle, prostatic gland and stomach (Figs. 5, 6 and 7).

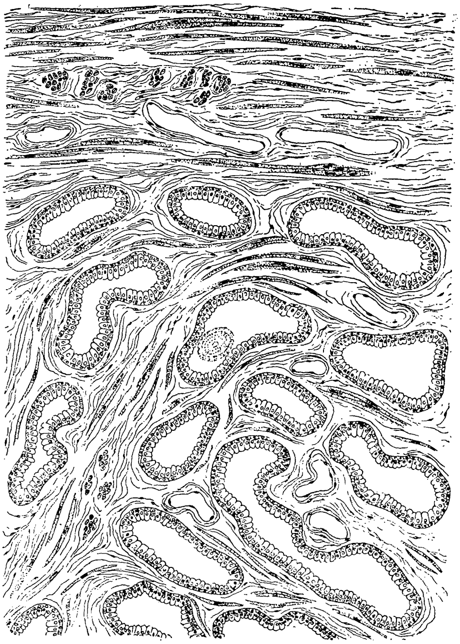
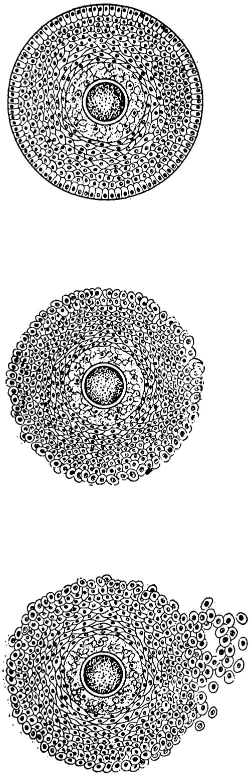


FIG. 4. Diagrammatic relation of the glandular units to the other tissues.

A change of environment through overgrowth or migration often stimulates or allows an attempt at differentiation into the specific tissue-cells for which the original reserve or regenerative cells (textoblasts) were apparently foreordained in the normal evolution of tissues. This is evident in cancerous new growths which have migrated into other tissues, and in regional lymphatic glands, which are the favorite locations of environmental change for such migrants.

Cellular regenerative reaction takes place in one or both of two ways; there is hyperplasia with or without differentiation. An hyperplasia with differentiation into specific tissue-cells may be called texto-typic in contradistinction to that without differentiation, which may be termed cytotypic. This occurs before and after migration.



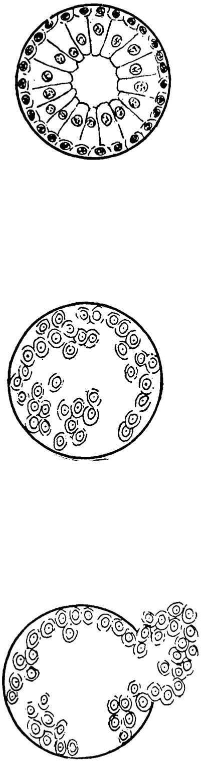
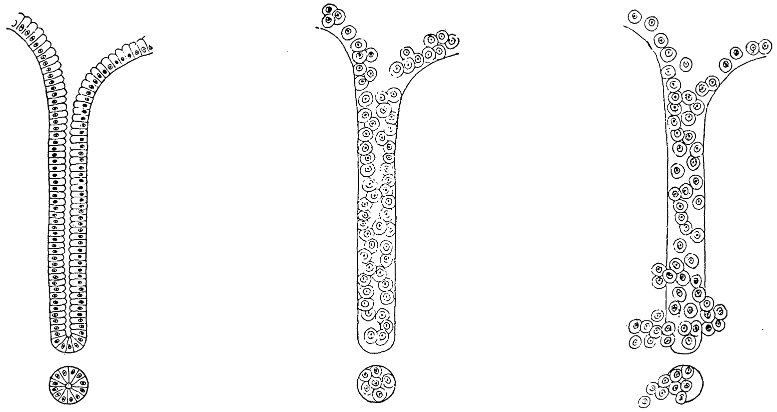


FIG. 5. The reaction to destruction of textocytes in the hair follicle. *A.* Primary pilo-cytoplasia. *B.* Secondary pilo-cytoplasia. *C.* Tertiary pilo-cytoplasia.

FIG. 6. The reaction to destruction of textocytes in the prostatic acinus. *A.* Primary adeno-cytoplasia. *B.* Secondary adeno-cytoplasia. *C.* Tertiary adeno-cytoplasia.

According to writers on the subject of cancer the principal criterion for the denotation of a condition by this term consists of the destructive migration of tissue-cells. Such neoplasms have been often considered to be direct derivatives of tissue-cells, because their cells sometimes resemble those of specific tissues of organs from which they have arisen. As a matter of fact the malignant neoplastic cells (neocytes) do sometimes resemble the



Primary Cytoplasia Secondary Cytoplasia Tertiary Cytoplasia

FIG. 7. The reaction to destruction of textocytes in the gastric tubules. *A*. Primary adeno-cytoplasia. *B*. Secondary adeno-cytoplasia. *C*. Tertiary adeno-cytoplasia.

specific tissue-cells of the site of origin, but this is not evidence that the tissue cells themselves have been converted into the cells, which at best never are morphologically and functionally identical with the original tissue-cells.

According to the observations of the writer, the cells which constitute cancer are the progeny of the partially differentiated or reserve cells (textoblasts) which have for their natural communistic function the protective restoration of the specific tissues when the latter have been destroyed. It may be asked, how can a condition which will certainly destroy the whole organism be the result of a protective principle? This perfectly natural question can only be answered by stating a general principle in biology, namely, that regenerative changes do not always consider the communistic adaptation of the whole organism. It is a manifestation of a principle which is inherent in cells, cytologic life being primary, and tissue or organic life secondary. Thus, the planarian in response to certain stimuli produces a new head when it already possesses one; the actinian produces a new mouth on the side of its body under certain regenerative conditions. Protective migration of animals as a result of food famine leads to their complete destruction not infrequently.

In the case of the human being there is no more fitting example of a fatal, protective communistic action of cells than that which occurs when a human being obtains a severe and destructive burn about the mouth or in the esophagus. Under such circumstances the fibroblasts in the region become hypertrophic, hyperplastic, differentiated and specialized into dense, contracting scar-tissue, which, if the destruction has been great enough, may, as a communistic, regenerative, protective process, inherent in the fibroblasts, completely close the orifice of the mouth or esophagus, the result of which is starvation and destruction of the whole organism. The fibroblast's evolutionary duty in the communism is that of replacing losses of other tissues, and the duty is performed in this incidence at the expense of its own life and the life of the organism. Thus, it may be seen that communistic life is secondary to the life of the cells even in such a wonderful and complex organization as the human body.

The hyperplasia or neoplasia does not even have to be migratory from a cellular standpoint to destroy the whole organism and thereby be clinically malignant; a term which has been utilized by the medical profession largely to differentiate cancer from other neoplastic conditions which are generally conceived of as benign. Thus, a fibroid tumor of the uterus may be clinically malignant and still not show cytologic signs of the malignancy so characteristic of cancer.

Biologically speaking, protection may be divided into types—cytotypic, textotypic, organotypic, systemotypic, organismotypic, familiotypic, raciotypic and speciotypic, etc. Cancer represents the cytotypic protection which is of primary importance in all protection of living protoplasm.

From a biological standpoint the three reactions of regenerative cells of tissues to antagonistic influences are hypertrophy and hyperplasia with differentiation, hyperplasia without differentiation, and hyperplasia with migration, with or without partial differentiation. These three conditions have been termed cytoplasias (conditions of cells) and have been numerically classified by the writer as primary (restauro-), secondary (expando-), and tertiary (migro-) cytoplasia. This classification is applicable to the regenerative cells of epithelial tissue of the mammary gland, prostatic gland, skin, hair follicle, stomach, fibrous connective tissue, erythrocytic tissue (red blood corpuscles) and lymphocytic tissue. These represent eight tissues out of possible nineteen or more known specific tissues in the human body. Doubtless there are other specific tissues in the human economy and perhaps some of those already mentioned may be eventually divided into other specific tissues. In all of the following tissues, adenotex, cardiomyotex, chondrotex, endotheliotex, epitheliotex, erythrotex, fibrotex, leucotex, leiomyotex, lipotex, lymphotex,, melanotex, myxotex, neurotex, osteotex, pilotex, rhabdomyotex and tendotex, with the exception of the neurotex and perhaps the myxotex, the fact has been demonstrated that all are regenerated after loss, the degree of regeneration varying considerably in the human body.

The following classification of the three biologic reactive phenomena which take place in the regenerative cells of tissues may be made:

Primary (restauro-)
Secondary (expando-)
Tertiary (migro-)

adeno-
cardiomyo-
chondro-
endothelio-
epithelio-
erythro-
fibro-
leuco-
leimyo-
leiomyo-
lympho-
melano-
myxo-
neuro-
osteo-
pilo-
rhabdomyo-
tendo-
etc..

cytoplasia.

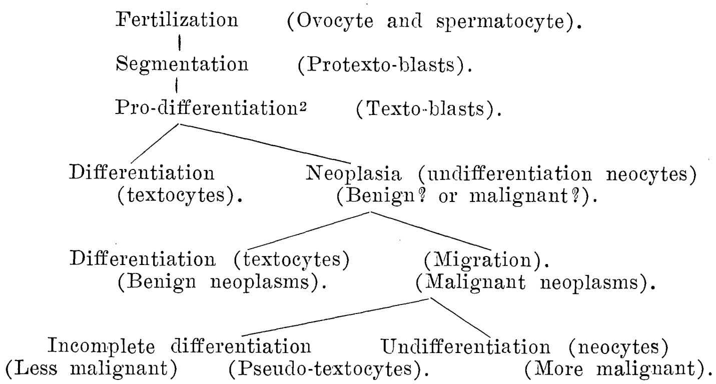
Such a nomenclature of known reactive facts has served the writer as a convenient, simple and practical, biologic, histologic and clinical terminology. The writer does not mean that these terms should be utilized to designate neoplasms. They apply only to the tissue-reaction, which is, after all, the essential thing to be considered. Animal and vegetable neoplasms represent only phases of such reaction.

From a clinical standpoint, a hypertrophy and hyperplasia with complete tissue differentiation (restaurocytoplasia) represents tissue regeneration, which is a benign condition, since it is normally reconstructive from a communistic standpoint instead of destructive. A hyperplasia without tissue differentiation (expandocytoplasia) represents a condition of the cells in which no one can foretell whether the cells will become differentiated into tissues, and thereby be constructive, or migrate and become destructive.

Such a condition is, therefore, in the presence of science, a questionable condition. Its benignancy or malignancy, in so far as the organization is concerned, with our present knowledge, can not be forecast. The probability of possible migration may be suspected from the frequent morphologic identity of these undifferentiated cells to the migratory cells of a known malignant or cancerous condition, the only difference being their location.

Biologically considered, primary cytoplasia represents a tissue regenerative condition, the secondary cytoplasia represents a neoplastic condition, and tertiary cytoplasia represents a neoplastic migration to regions foreign to the cells in question. The whole field of tissue replacement, tissue regeneration and benign and malignant (cancerous) neoplasmata (new growths) is comprehended in these three groups.

The following diagram represents the relation of malignant (cancerous) and so-called benign neoplasms to the evolution and organization of the human body:


Fertilization (Ovocyte and spermatocyte).
Segmentation (Protexto-blasts).
Pro-differentiation[2] (Texto-blasts).
Differentiation (textocytes).
Neoplasia (undifferentiation neocytes) (Benign? or malignant?).
Differentiation (textocytes) (Benign neoplasms).
(Migration). (Malignant neoplasms).
Incomplete differentiation (Less malignant) (Pseudo-textocytes).
Undifferentiation (neocytes) (More malignant).

Briefly, in conclusion, the writer makes the following generalizations from his experience in his studies of cancer's place in general biology:

1. All multicellular organisms represent communisms of cells which have divided their labors and become specialized and differentiated to form tissues.

2. Nature has provided for the regeneration of most, if not all, tissues when the tissues are partially destroyed by antagonistic forces.

3. In many animal and vegetable tissues the regenerative cells respond to tissue-destruction in three degrees, *i. e.*, hypertrophy, hyperplasia and migration.

4. During hyperplasia with or without migration the cells sometimes attempt to differentiate.

5. Limited hyperplasia with complete differentiation produces tissue replacement. Unlimited hyperplasia without complete differentiation produces the so-called malignant neoplasms.

6. Cancer represents an unlimited hyperplasia of regenerative cells of tissues plus migration without complete differentiation.

7. Regeneration (hyperplasia) without differentiation is a cytotypic protective process.

8. Regeneration (hyperplasia) with differentiation is a textotypic protective process.

9. Cancer is a cytotypic instead of a textotypic protective process.

10. In nature cytotypic protective processes are sometimes fatal to the communism of which the reactive cells are a part.

11. All of the reactions may be designated by a simple biologic terminology which standardizes clinical, histologic and biologic facts.

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[2] The stage of pro-differentiation exists prenatally and postnatally and may be distinguished terminologically by calling the prenatal cells of segmentation protextoblasts and the regenerative postnatal cells textoblasts.

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